IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC,	)	
Plaintiffs,	)	C.A. No. 06-286-GMS
v.	)	
BARR LABORATORIES, INC.,	)	**REDACTED PUBLIC VERSION**
Defendant.	)	

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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I. BACKGROUND

A. Proposed Findings of Fact

(1) The Parties and Patents-In-Suit

1. Plaintiff Aventis Pharmaceuticals Inc. ("Aventis"), a subsidiary of Sanofi-Aventis SA, is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807.

2. Plaintiff Sanofi-Aventis US LLC ("Sanofi-Aventis"), also a subsidiary of Sanofi-Aventis SA, is a limited liability company organized and existing under the laws of the State of Delaware, with its principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807.

3. Barr agrees that Defendant Barr Laboratories, Inc. ("Barr") is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 223 Quaker Road, Pomona, New York 10970. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 3).

4. Barr agrees that U.S. Application Number 08/678,465, from which United States Patent No. 5,976,573 ("the '573 patent") issued, was filed on July 3, 1996. The '573 patent issued on November 2, 1999, to Soo-Il Kim. The USPTO shows that the '573 patent was assigned to Rôrer Pharmaceutical Products Inc. ("RPR"), a predecessor-in-interest to Aventis. The USPTO shows that by assignment, through a chain of predecessors-in-interest, Aventis is the present owner of the '573 patent. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 8).

5. The '573 patent is entitled "Aqueous-based Pharmaceutical Composition."

6. Barr agrees that the '573 patent will expire on July 3, 2016. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 9).

7. Barr agrees that U.S. Application Number 09/315,454, from which United States Patent No. 6,143,329 ("the '329 patent") issued, was filed on May 20, 1999. The '329 patent issued on November 7, 2000, to Soo-Il Kim. The USPTO shows that the '329 patent was assigned to RPR. The USPTO shows that by assignment, through a chain of predecessors-in-interest, Aventis is the present owner of the '329 patent. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 10).

8. The '329 patent is entitled "Aqueous-based Pharmaceutical Composition."

9. The '329 patent claims priority to the parent application of the '573 patent, which was filed on July 3, 1996. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 11).

10. Barr agrees that the '329 patent will expire on July 3, 2016. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 12).

11. Barr agrees that, other than the claim of priority set forth in col. 1, lines 4-10 of the '329 patent, the '573 patent and the '329 patent share a common specification that is substantively the same for both patents. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 13).

12. Sanofi-Aventis is the holder of approved New Drug Application ("NDA") No. 20-468 for once-daily Nasacort® AQ nasal spray (triamcinolone acetonide, 0.055 μg/spray), indicated for the treatment of allergic rhinitis.

13. Barr agrees that NDA No. 20-468 was approved on May 20, 1996 and that Sanofi-Aventis is the owner of NDA 20-468. (*See* App. A, Parties' Statement of Uncontested Facts, ¶¶ 18, 15).

14. The '573 and '329 patents are listed in the Food and Drug Administration ("FDA") publication *Approved Drug Products with Therapeutic Equivalence Evaluation* (the

"Orange Book") in relation to Nasacort® AQ nasal spray. Barr agrees that the FDA's Orange Book lists the '573 patent and the '329 patent in connection with NDA 20-468. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 19).

15. Barr agrees that Aventis is the manufacturer of Nasacort® AQ. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 14).

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(*See* App. A, Parties' Statement of Uncontested Facts, ¶ 20).

17. Barr agrees that, by letter dated March 20, 2006, and received March 23, 2006, Barr notified Plaintiffs of the filing of ANDA 78-104 with the Paragraph IV certification. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 21).

18. Plaintiffs filed this lawsuit against Barr on May 2, 2006, alleging infringement of the '573 and '329 patents under 35 U.S.C. § 102(e)(2)(A).

19. Plaintiffs are asserting claims 5, 6, 7, 8, 21, 22, 23, 24, 26, 27, 28, 34, and 35 of the '573 patent against Barr in this case. Claims 5, 6, 7, and 8 cover aqueous triamcinolone acetonide pharmaceutical compositions which are capable of being sprayed into the nasal cavity of individuals. Claims 21, 22, 23, 24, 26, 27, and 28 cover methods for treating allergic rhinitis

in individuals comprising applying aqueous triamcinolone acetonide pharmaceutical compositions to the mucosal surfaces of the nasal cavities of individuals. Claims 34 and 35 cover methods for applying solid particles of triamcinolone acetonide to the mucosal surfaces of the nasal cavities comprising spraying doses of an aqueous pharmaceutical composition containing the medicament into each of the nasal cavities.

20. Plaintiffs are asserting claims 13, 14, 15, 16, 23, 24, 25, and 26 of the '329 patent against Barr in this case. Claim 13 covers an article of manufacture comprising a thixotropic aqueous triamcinolone acetonide pharmaceutical composition which is capable of being sprayed into the nasal cavity of an individual. Claims 14, 15, 16, 23, and 24 cover methods for treating allergic rhinitis in individuals comprising the administration of aqueous thixotropic triamcinolone acetonide pharmaceutical composition to the individuals. Claims 25 and 26 cover methods for delivering aqueous thixotropic pharmaceutical compositions comprising triamcinolone acetonide to each of the mucosal surfaces of the anterior regions of the nose, the frontal sinus and the maxillary sinuses and on each of the mucosal surfaces which overlie the turbinates covering the conchas.

(2) Barr's ANDA Product

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(3) Allergic Rhinitis

25. Barr agrees that allergic rhinitis is the consequence of an exaggerated reaction by the body's immune system as a response to foreign substances (antigens) in the nasal cavity. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 4).

26. Barr agrees that seasonal and perennial allergic rhinitis are associated with sneezing, nasal drainage, itching and congestion. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 5).

27. Barr agrees that seasonal allergic rhinitis, sometimes known as hay fever, results from foreign substances (antigens) found in pollen from trees, grasses, and weeds and occurs during certain times of the year. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 6).

28. Barr agrees that perennial allergic rhinitis may occur year-round and results from antigens such as animal dander, mold spores, and dust mites that are present in the environment independent of the time of year. Perennial allergic rhinitis can coexist with seasonal exacerbations of the symptoms. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 7).

(4) Nasal Anatomy

29. Air enters the nasal cavity from outside the body through the anterior (or external) nares, commonly known as the nostrils.

30. The anterior nose or nasal vestibule (the portion of the nose anterior to the nasal valve or internal ostium) is generally external to the skull, consists of bone and cartilage, is covered externally with skin and lined internally with mucous membranes.

31. Beginning with the anterior nose, the entire nasal cavity is separated bilaterally by a structure known as the nasal septum.

32. The anterior nose is the narrowest portion of the airway (approximately 0.3 cm^3 on each side). The anterior portion of the nose is covered by squamous epithelial cells, which have no cilia, and have large hairs internally. Unlike the portion of the nose posterior to the nasal valve, the anterior portion of the nose does not clear mucous through mucociliary clearance.

33. The nasal valve, located at the lower border of the lateral nasal cartilage, separates the portion of the nose that generally does not clear through mucociliary clearance from the portion of the nose that does.

34. The nasal cavity is located posterior to the nasal valve and anterior to the pharynx. The nasal cavity lies below the cranium and above the mouth. It is separated from the mouth by the palate, which is a generally horizontal plate of bone and tissue running along the top of the mouth and the bottom of the nasal cavity.

35. The nasal septum divides the nasal cavity into right and left sides. The nasal cavity is approximately 10 to 12 cm long, has a volume of approximately 15 milliliters, and has a surface area of approximately 150 cm^2.

36. As air flows back from the nasal valve, it flows by the conchas covering the turbinate bones. Each concha consists of a turbinate bone and a recess (or meatus) beneath the turbinate bone. The turbinate bones are located at the sidewall of each nasal cavity and they extend horizontally along the sidewall, forming shelf-like structures on the sidewall of the nasal cavity. The conchas have a generally spiral shape, which causes the airflow to be redirected.

37. The inferior turbinates are the longest of the turbinates and redirect more airflow than the others, moisten and heat the flowing air, and filter the inhaled air. The middle turbinates are shorter and buffer the sinuses from inhaled air. Most of the airflow from inhaled air passes between the inferior and middle turbinates. The superior turbinates are the shortest of the three turbinates and protect the olfactory bulb from airflow.

38. Four paranasal sinuses connect to the internal nose through small orifices called ostia. The sinuses are air-filled spaces located between, behind, and beneath the eyes. The four paranasal sinuses are the frontal sinuses, sphenoidal sinuses, maxillary sinuses, and ethmoidal sinuses.

39. The frontal sinuses are located over the eyes in the frontal bone. The sphenoidal sinuses are located in the sphenoid bone at the center of the base of the front portion of the skull, behind the eyes. The maxillary sinuses are located under the eyes in the maxillary bones (which form a part of the cheeks). Finally, the ethmoid sinuses are located within the ethmoid bone between the nose and eyes. Of the four, the frontal and maxillary sinuses are relatively large; the sphenoid and ethmoid sinuses are relatively small.

40. The entrance to the frontal sinus is at the anterior osteomeatal complex, at the upper aspect of the middle turbinate. Some air from each inspiration reaches the frontal

sinus, and it is therefore possible that some part of a dose of an aqueous intranasal spray would reach that point.

41. There is little deposition of medicament from aqueous intranasal steroid sprays before the nasal valve, as aqueous intranasal steroid sprays products are designed with a nozzles long enough to pass beyond the nasal valve. The posterior portion of the turbinates is the primary location of particle impact for aqueous intranasal steroid sprays.

42. Mucous membranes (or nasal mucosa) line the nasal cavity and sinuses. Mucous membranes consists of many layers, including ciliated pseudostratified columnar epithelium, basement membrane, lamina propria ("submucosa") with arterio-venous anastomoses, glands, and venous sinusoids, and periosteum.

43. The top layer of the mucous membrane structure is covered by a sticky gel layer formed by a blanket of mucous. The sticky gel layer traps foreign particles including bacteria, viruses, and allergens.

44. Below the gel layer is a sol (or aqueous) periciliary layer. The sol layer functions both to transport the mucous layer through the beating of the cilia of the ciliated pseudostratified columnar epithelium and provide antimicrobial protection through proteins secreted by serous cells.

45. Below the fluid layers is the columnar epithelium, a layer separated from deeper mucosal structures by the basement membrane. The epithelium consists of ciliated columnar epithelial cells, nonciliated columnar epithelial cells, goblet cells, and basal cells. The goblet cells secrete mucous that overlays the mucous membrane.

46. Cilia of the ciliated columnar epithelial cells beat in a wavelike pattern through the sol layer. The cilia move the upper mucous layer and foreign particles stored in the

mucous layer to the rear of the nasal cavity and the pharynx. When foreign particles reach the pharynx, they can be removed from the respiratory tract by either being swallowed or expectorated.

47. The anterior portions of the turbinates are ciliated.

48. Nasal mucociliary clearance is a part of the nose's defense against foreign particles. Foreign particulate matter may deposit on the nasal mucosa after inhalation, then will stick to the outer mucous layer and be moved posteriorly through the nasal cavity to the nasopharynx by the mucociliary clearance forces.

49. The movement of mucus posteriorly through the nasal cavity is closely related to the beating pattern of the cilia of the sol layer. In humans, the cilia typically beat at a frequency of 10-20 Hz, which corresponds to approximately 1000 strokes per minute. A stroke consists of a rapid forward movement of the cilia and a slower return movement. During the forward movement, the tips of outstretched cilia reach up into the upper sticky mucous layer to provide the propulsive force. Cilia beating in the sol layer transport the mucous layer only by the tips of the cilia during the propulsive portion of the stroke. During the return movement, the cilia are bent down and return only through the sol layer of the mucous. The coordinated strokes of the cilia move the mucous layer at a flow rate of about one centimeter per minute.

50. Approximately one quart of mucus is secreted from the nasal mucosa of a normal, resting nose over a 24-hour period. Thus, humans are constantly clearing the nasal mucosa of trapped particles which are swallowed unconsciously throughout the day. It generally takes approximately 10 to 30 minutes to clear anterior particles to the pharynx, and typically less than 15 minutes.

51. Saccharine placed on the anterior turbinates generally leads to clearance in about 10 to 15 minutes.

52. The surface of the mucous membrane structure is a blanket of hydrophobic mucous; thus, aqueous fluids that deposit on that layer would not be diluted.

53. There is very little turnover in the aqueous periciliary layer, which means that substances that enter that layer are not continuously diluted. This is shown in the long residence time that proteins have in the aqueous periciliary layer.

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55. Excipient influences are also important when material enters the aqueous periciliary layer and help maintain particles in place.

(5) PET Testing

56. Dr. Marc Berridge performed positron emission tomography ("PET") studies to determine the deposition pattern and retention of Nasacort® AQ. Portions of the results of Dr. Berridge's 1996 PET study of Nasacort® AQ were the basis for the information provided in the '573 patent at column 11, line 7 through column 12, line 54 and in the '320 patent at column 11, line 15 through column 12, line 64.

57. PET is a nuclear imaging technique in which a radioactive material is administered to the patient, then quantitatively measured in the body during one or a number of sequential observation periods by an external detector, generally a PET camera. PET is an accepted research and diagnostic technique in the field of nuclear medicine and is considered the best nuclear imaging technique available for quantifying the amount of drug deposited in the body and tracking that deposited drug over a period of time.

58. Dr. Berridge's PET testing allowed for three dimensional spatial sampling of nasal regions, which resulted in accurate definition of the regions of interest and quantification of the amount of labeled drug located in each of those regions of interest over an extended period of time.

59. In all PET studies, regions of interest are defined in space in three dimensions to represent the anatomic areas in which it was desired to know the deposition and kinetics of the radio-labeled material.

60. In Dr. Berridge's 1996 PET study, three-dimensional regions of interest were defined first as a group of 104 small cubes that included all of space occupied by the anatomic spatial regions included in the study. These regions were compared with an MRI scan of the patient after alignment of the MRI with the PET scan and were assigned to anatomical

regions according to their positions on the scan. Separate regions were identified for the frontal sinus, maxillary sinuses, anterior nose, and turbinates (among other regions).

61. In Dr. Berridge's 1996 study, the definition of regions of interest in the PET scanner divided the turbinates (concha) vertically into two portions, the superior and inferior regions. Anatomically, the turbinates and conchas are actually three structures (superior, middle, and inferior). The regions used do not correspond to the anatomic folds of the turbinates, rather they represent an even division of the entire region into two portions. For the purposes of demonstrating the extent of penetration of the drug, that division provided sufficient definition.

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66. For all of Dr. Berridge's PET studies, the volunteers were administered radiolabeled Nasacort® AQ spray according to the package insert directions.

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68. In Dr. Berridge's 1996 PET study, three subject data sets were obtained.

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70. The data from Dr. Berridge's 1996 PET study demonstrated that Nasacort® AQ resisted clearance of the active ingredient from the nasal region as compared to known clearance rates expected for solutions or materials which are cleared by mucociliary action. Thus, the data showed that the composition resists being cleared from mucosal surfaces by the inherent mucociliary forces which are present in the nasal cavity.

71. The data from all subject sets of Dr. Berridge's 1996 PET study showed that deposition of the drug occurred on all target tissues (frontal and maxillary sinus regions, frontal cavity region, and all concha regions) and that retention of drug in those regions was observed for a sufficient period of time to conclude that mucociliary clearance was successfully resisted.

72. The data from Dr. Berridge's 1996 PET study (both individual and collective) show that TAA in Nasacort® AQ was deposited in the anterior regions of the nose (frontal cavity/vestibule). The time course of the deposition shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (no more than 30 minutes) and further shows that at least some of the deposited dose remains in the region for at least about 1 hour.

73. The data from Dr. Berridge's 1996 PET study (both individual and collective) show that TAA in Nasacort® AQ was deposited in the inferior concha (turbinate) region. The time course of the deposition shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (no more than 30

minutes) and further shows that at least some of the deposited dose remained in the region for at least about 1 hour.

74. The data from Dr. Berridge's 1996 PET study (both individual and collective) show that TAA in Nasacort® AQ was deposited in the superior concha (turbinate) region. The time course of the deposition shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (no more than 30 minutes) and further shows that at least some of the deposited dose remained in the region for at least about 1 hour.

75. The data from Dr. Berridge's 1996 PET study (both individual and collective) show that TAA in Nasacort® AQ was deposited in the frontal sinus region. The time course of the deposition shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (no more than 30 minutes) and further shows that at least some of the deposited dose remains in the region for at least about 1 hour.

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77. The data from Dr. Berridge's 1996 PET study (both individual and collective) show that TAA in Nasacort® AQ was deposited in the maxillary sinus region. The

time course of the deposition shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (no more than 30 minutes) and further shows that at least some of the deposited dose remained in the region for at least about 1 hour.

78. The nasal cavity, as defined for this case, includes the anterior regions of the nose (the frontal cavity, upper and lower), the turbinates which overlie the concha, the maxillary sinuses and the frontal sinuses. The data from Dr. Berridge's PET studies in aggregate shows that TAA in Nasacort® AQ was deposited in the entire region. The time course of the deposition shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (no more than 30 minutes) and further shows that at least some of the deposited dose remained in the region for at least about 1 hour.

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II. INFRINGEMENT OF THE '573 AND '329 PATENTS

A. Proposed Conclusions of Law

97. A patent owner has the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

98. Under 35 U.S.C. § 271(e)(2)(A), it is an act of patent infringement to file an ANDA for a drug claimed in a patent (or the use of which is claimed in a patent) in order to market the drug before expiration of the patent. *Glaxo v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997). *See also Abbott Labs. v. Torpharm, Inc.*, 503 F.3d 1372, 1378 (Fed. Cir. 2007) ("As we have held numerous times, the filing of a paragraph IV certification is itself an act of infringement if the purpose of the ANDA submission is to obtain the FDA's approval to engage in the commercial manufacture, use, or sale of a patented drug before expiration of the drug patent.") (citations omitted). Thus, "the district court's infringement analysis in a Hatch-Waxman suit is no different than that in any other patent infringement suit." *Id.* at 1379 (citing *Glaxo*, 110 F.3d at 1569.

99. A determination of patent infringement requires a two-step analysis. First, the court determines the scope and meaning of the patent claims asserted. Second, the properly construed claims are compared to the allegedly infringing device. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (*en banc*).

100. A finding of direct infringement requires a determination that every claim limitation is found in the accused product. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997).

101. A finding of inducement of infringement under 35 U.S.C. § 271(b) requires two showings: first, that an accused party induced another party to commit infringing acts, and second, that the accused party knew or should have known its actions would induce actual infringement. *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990).

102. The law does not require that all acts that result from the inducing activity result in infringement, only that the acts of inducement result in infringement at least part of the time. *See Hilgraeve Corp. v. Symantec Corp.*, 265 F.3d 1336, 1343 (Fed. Cir. 2001) ("the sale of a device may induce infringement of a method claim, even if the accused device is capable of non-infringement modes of operation in unusual circumstances.") *See also Alcon Labs., Inc. v. Bausch & Lomb, Inc.*, 52 U.S.P.Q. 2d 1927 (N.D. Tex. 1999) (finding inducement despite the fact that "the vast majority of uses of the generic will be prophylactic, and the prevention – as opposed to the treatment – of inflammation and infection is not claimed in the patent."); *Purdue Pharma, L.P. v. F.H. Faulding and Co.*, 48 F. Supp. 2d 420, 439 (D. Del. 1999) (finding infringement where each element of the claim is present in some patients).

103. "While proof of intent [to induce infringement] is necessary, direct evidence is not required; rather circumstantial evidence may suffice." *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir.), *cert. denied*, 488 U.S. 968 (1988). "The requisite intent to induce infringement may be inferred from all of the circumstances." *Id.* at 669.

104. Instruction, advertising and promotion may constitute active steps, knowingly taken to bring about infringement of the patents. *Scott Paper Co. v. Moore Business Forms, Inc.*, 594 F. Supp. 1051, 1082 (D. Del. 1984) (advertisement, promotion and sales of

business forms whose only known use was in practicing patented method constituted active inducement to infringe).

105. The Court has construed the term "pharmaceutically effective amount" to mean "an amount that exerts the pharmacological action of the medicament."

106. The Court has limited the term thixotropic to refer to those properties described in specific claims or, in the absence of properties described in a specific claim, those properties described in the specification.

107. Among other passages regarding the definition of "thixotropic", the Court identified the abstract of the patents-in-suit, which states (among other things):

> ... (i) the viscosity of the position [sic: composition] in unsheared form is relatively high, with the composition being in a gel-like form; (ii) as the composition is subjected to shear (shaken) in preparation for spraying, the viscosity of the composition becomes relatively low and such that the composition in the form of a mist flows readily into the nasal passages for deposit on the mucosal surfaces of the nasal cavity; and (iii) in deposited form on the mucosal surfaces, the viscosity of the composition is relatively high and such that it resists being cleared from the mucosal surfaces by the inherent mucocillary forces which are present in the nasal cavity ...

108. The Court has construed the term "the viscosity of the composition in unsheared form is relatively high, with the composition being a gel having said particles suspended therein" to mean "the viscosity of the composition at rest is higher than the shear viscosity and sufficiently high to hold and maintain the particles of TAA suspended and dispersed substantially uniformly in the composition."

109. The Court has construed the term "in deposited form on the mucosal surfaces, the viscosity of the composition is relatively high and such that it resists being cleared from the mucosal surfaces by the inherent mucocillary forces which are present in the nasal

cavity" to mean "following deposition on the mucosal surfaces, the composition returns to its unsheared viscosity, which is relatively high and such that it resists being swept away by the mucocillary forces present in the nasal cavity."

110. The Court has construed the term "in deposited form on the mucosal surfaces, the viscosity of the composition is about 400 to about 800 cp and such that it resists being cleared from the mucosal surfaces by the inherent mucocillary forces which are present in the nasal cavity" to mean "following deposition on the mucosal surfaces, the composition returns to its unsheared viscosity, which is approximately 400 to 800 cp, when measured according to the method disclosed in the specification, and such that it resists being swept away by the mucocillary forces present in the nasal cavity."

111. The Court has construed the term "the mucosal surfaces of the nasal cavity" to mean "the mucous membranes that line, among other things, the anterior regions of the nose, the turbinates which overlie the concha, the maxillary sinuses, and the frontal sinus."

112. The Court has construed the terms "for deposit on the on the mucosal surfaces of the nasal cavity" and "in deposited form on the mucosal surfaces" to mean that the medicament is deposited on all of the mucosal surfaces.

B. Proposed Findings of Fact

(1) U.S. Patent No. 5,976,573

(a) Claim 5 of the '573 Patent

113. Claim 5 of the '573 patent covers:

> An aqueous pharmaceutical composition which is capable of being sprayed into the nasal cavity of an individual, which is odorless, propellant-free, and has a pH of about 4.5 to about 7.5, and which comprises: (A) at least about 85 wt. % of water; (B) about 0.001 to about 2 wt. % of solid particles of triamcinolone acetonide medicament; (C) about 1 to about 5 wt. % of a suspending agent

comprising a mixture of about 85 to 95 wt. % of microcrystalline cellulose and about 5 to about 15 wt. % of carboxymethyl cellulose based on the weight of the mixture, the amount of suspending agent being effective to maintain said solid particles dispersed uniformly in the composition and to impart to the composition the following thixotropic properties: (i) the viscosity of the composition in unsheared form is about 400 to about 800 cp; (ii) as the composition is subjected to shear (shaken) in preparation for spraying, the viscosity of the composition is about 50 to about 200 cp and such that the composition in the form of a mist flows readily into the nasal passages for deposit on the mucosal surfaces of the nasal cavity; and (iii) in deposited form on the mucosal surfaces, the viscosity of the composition is about 400 to about 800 cp and such that it resists being cleared from the mucosal surfaces by the inherent mucocillary forces which are present in the nasal cavity; and (D) about 0.004 to about 0.02 wt. % of a quaternary ammonium compound that has anti-microbial properties; and (E) about 0.01 to about 0.5 wt. % of a chelating agent.

114. Barr's ANDA product meets each and every limitation of claim 5 of the '573 patent, as set forth below.

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142. From the thixotropic nature of formulations that fall within the scope of the asserted claims, it is reasonable to conclude that post-shear "deposited form" viscosity recovers to its initial viscosity.

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147. Data from Dr. Berridge's PET studies show that Nasacort® AQ resisted clearance from the mucosal surfaces of the nasal cavity by inherent mucociliary forces which were present in the nasal cavity.

148. The time course of the deposition in Dr. Berridge's 1996 PET study shows that at least some of the deposited dose of drug was retained longer than the standard expected time for mucociliary clearance (due to which, clearance would be expected to occur in no more than 30 minutes) and further shows that at least some of the deposited dose remained in the

anterior regions of the nose for at least about 1 hour; on the inferior concha for at least about 1 hour; on the superior concha for at least about 1 hour; in the frontal sinus for at least about 1 hour; and in the maxillary sinuses for at least about 1 hour.

149. In the absence of any resistance of clearance from the mucosal surfaces and in aqueous solution or suspension, a rapid and complete clearance of drug from the tissues would be expected, with a half-time of 15 minutes or less, completing the process within 30 minutes. In Dr. Berridge's 1996 PET study, a much slower clearance rate of Nasacort® AQ was observed.

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154.

REDACTED

155.

REDACTED

156.

157. Benzalkonium chloride is an example of a quaternary ammonium compound that has antimicrobial properties.

158.

REDACTED

159.

REDACTED

160. Edetate disodium is also known as disodium ethylenediamine tetraacetate (or disodium EDTA).

161.

REDACTED

(b) Claim 6 of the '573 Patent

162. Claim 6 of the '573 patent covers: "A composition according to claim 5 wherein said quaternary ammonium compound is benzalkonium chloride and said chelating agent is disodium ethylenediamine tetraacetate."

163. Barr's ANDA product meets each and every limitation of claim 6 of the '573 patent, as set forth below.

164. Barr's ANDA product meets each and every limitation of claim 5 of the '573 patent. (*See* ¶¶ 113-161).

165.

REDACTED

166. REDACTED

(c) Claim 7 of the '573 Patent

167. Claim 7 of the '573 patent covers: "A composition according to claim 5 having about 0.001 to about 0.01 wt. % of dispersing agent which is effective in wetting the particles of medicament."

168. Barr's ANDA product meets each and every limitation of claim 7 of the '573 patent, as set forth below.

169. Barr's ANDA product meets each and every limitation of claim 5 of the '573 patent. (*See* ¶¶ 113-161).

170. REDACTED

(d) Claim 8 of the '573 Patent

171. Claim 8 of the '573 patent states covers: "A composition according to claim 7 wherein said dispersing agent is Polysorbate 80™."

172. Barr's ANDA product meets each and every limitation of claim 8 of the '573 patent, as set forth below.

173. Barr's ANDA product meets each and every limitation of claim 7 of the '573 patent. (*See* ¶¶ 167-170).

174. REDACTED

175. REDACTED

(e) Claim 21 of the '573 Patent

176. Claim 21 of the '573 patent covers:

> A method for treating allergic rhinitis in an individual comprising applying to the mucosal surfaces of the nasal cavities of an individual a composition according to claim 5 by spraying a dose of the composition into each of the nasal cavities of the individual, said dose containing a pharmaceutically effective amount of said medicament and depositing pharmaceutically effective amounts of the medicament on each of the mucosal surfaces of the anterior regions of the nose, the frontal sinus and the maxillary sinuses and on each of the mucosal surfaces which overlie the turbinates covering the conchas and such that pharmaceutically effective amounts of the medicament are retained on each of said mucosal surfaces for at least about an hour.

177. Use of Barr's ANDA product according to Barr's proposed labeling meets each and every limitation of claim 21 of the '573 patent, as set forth below.

178. Use of Barr's ANDA product in the manner directed in Barr's proposed labeling will cause users to infringe claim 21 of the '573 patent.

REDACTED

179. Barr's proposed labeling provides physicians and patients with information about Barr's ANDA product and instructions for using the product.

180. Barr's ANDA product meets each and every limitation of claim 5 of the '573 patent. (*See* ¶¶ 113-161).

181.

REDACTED

182. REDACTED

183. REDACTED

184. REDACTED

185. REDACTED

186. REDACTED

187. REDACTED

188. REDACTED

189. REDACTED

190. REDACTED

191. REDACTED

192. REDACTED

193. Dr. Berridge's PET studies show that, when used according to the package insert, pharmaceutically effective amounts of TAA in Nasacort® AQ are deposited on each of the mucosal surfaces of the anterior regions of the nose, the frontal sinus and the maxillary sinuses and on each of the mucosal surfaces which overlie the turbinates covering the conchas and are retained on each of the said mucosal surfaces for at least about an hour.

194. REDACTED

(f) Claim 22 of the '573 Patent

195. Claim 22 the '573 patent covers: "A method according to claim 21 wherein said quaternary ammonium compound is benzalkonium chloride, and said chelating agent is disodium ethylenediamine tetraacetate."

196. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 22 of the '573 patent, as set forth below.

197. Use of Barr's ANDA product REDACTED will cause users to infringe claim 22 of the '573 patent.

REDACTED

198. Use of Barr's ANDA product REDACTED ; meets each and every limitation of claim 21 of the '573 patent. (*See* ¶¶ 176-194).

199. REDACTED

200. REDACTED

(g) Claim 23 of the '573 Patent

201. Claim 23 of the '573 patent covers: "A method according to claim 21 wherein the composition which is applied to said surfaces includes about 0.001 to about 0.01 wt. % of dispersing agent which is effective in wetting the particles of medicament."

202. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 23 of the '573 patent, as set forth below.

203. Use of Barr's ANDA product REDACTED will cause users to infringe claim 23 of the '573 patent.

REDACTED

204. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 21 of the '573 patent. (*See* ¶¶ 176-194).

205. REDACTED

(h) Claim 24 of the '573 Patent

206. Claim 24 of the '573 patent states covers: "A method according to claim 23 wherein said dispersing agent is Polysorbate 80™."

207. Use of Barr's ANDA product according to Barr's proposed labeling meets each and every limitation of claim 24 of the '573 patent, as set forth below.

208. Use of Barr's ANDA product REDACTED, will cause users to infringe claim 24 of the '573 patent.

REDACTED

209. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 23 of the '573 patent. (*See* ¶¶ 201-205).

210. REDACTED

211. REDACTED

(i) Claim 26 of the '573 Patent

212. Claim 26 of the '573 patent covers: "A method according to claim 21 wherein said composition is applied once daily to each of the nasal cavities of the individual in an amount which includes about 100 to about 130 mcg of said medicament."

213. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 26 of the '573 patent, as set forth below.

214. Use of Barr's ANDA product REDACTED

, will cause users to infringe claim 26 of the '573 patent.

REDACTED

215. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 21 of the '573 patent. (*See* ¶¶ 176-194).

216.

REDACTED

217.

REDACTED

(j) Claim 27 of the '573 Patent

218. Claim 27 of the '573 patent covers: "A method according to claim 26 wherein said composition is applied by use of a precompression pump."

219. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 27 of the '573 patent, as set forth below.

220. Use of Barr's ANDA product REDACTED will cause users to infringe claim 27 of the '573 patent.

REDACTED

221. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 26 of the '573 patent. (*See* ¶¶ 212-217).

222.

REDACTED

223.

REDACTED

224.

REDACTED

(k) Claim 28 of the '573 Patent

225. Claim 28 of the '573 patent covers:

> The method according to claim 26 wherein said composition comprises triamcinolone acetonide, a mixture of microcrystalline cellulose and carboxymethyl cellulose sodium, Polysorbate 80™, disodium ethylenediamine tetraacetate, benzalkonium chloride, dextrose and purified water.

226. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 28 of the '573 patent, as set forth below.

227. Use of Barr's ANDA product REDACTED will cause users to infringe claim 28 of the '573 patent.

REDACTED

228. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 26 of the '573 patent. (*See* ¶¶ 212-217).

229. REDACTED

(l) Claim 34 of the '573 Patent

230. Claim 34 of the '573 patent covers:

> A method for applying solid particles of triamcinolone acetonide to the mucosal surfaces of the nasal cavities comprising spraying a dose of an aqueous pharmaceutical composition containing said medicament into each of the nasal cavities, said dose containing a pharmaceutically effective amount of triamcinolone acetonide, said composition including also a suspending agent in an amount which is effective in maintaining said particles dispersed uniformly in the composition and in imparting to the composition thixotropic properties such that pharmaceutically effective amounts of triamcinolone acetonide are deposited on each of the mucosal surfaces of the anterior regions of the nose, the frontal sinus and the maxillary sinuses, and on each of the mucosal surfaces which overlie the turbinates covering the conchas and such that portions of said amounts are retained on each of said mucosal surfaces for at least about an hour.

231. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 34 of the '573 patent, as set forth below.

232. Use of Barr's ANDA product REDACTED will cause users to infringe claim 34 of the '573 patent. REDACTED

233. REDACTED

234. REDACTED

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238. REDACTED

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240. REDACTED

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245. REDACTED

246. REDACTED

REDACTED

247. REDACTED

248. REDACTED

(m) Claim 35 of the '573 Patent

249. Claim 35 of the '573 patent covers: "A method according to claim 34 wherein the viscosity of the composition in unsheared form is about 400 to about 1000 centipoises and wherein the viscosity of the composition when shaken is about 50 to about 200 centipoises."

250. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 35 of the '573 patent, as set forth below.

251. Use of Barr's ANDA product REDACTED will cause users to infringe claim 35 of the '573 patent.

REDACTED

252. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 34 of the '573 patent. (*See* ¶¶ 231-248).

253. REDACTED

254. REDACTED

(2) U.S. Patent No. 6,143,329

(a) Claim 13 of the '329 Patent

255. Claim 13 of the '329 patent covers:

> An article of manufacture comprising:
> (A) a thixotropic aqueous pharmaceutical composition which is capable of being sprayed into the nasal cavity of an individual, which is propellant-free and has a pH of about 4.5 to 7.5, and which comprises (a) triamcinolone acetonide; (b) a mixture of microcrystalline cellulose and carboxymethylcellulose sodium; (c) Polysorbate 80; (d) disodium ethylenediamine tetraacetate; (e) benzalkonium chloride; (f) dextrose; and (g) purified water;
> (B) a vessel which contains said composition; and
> (C) a precompression pump associated with the vessel and which is capable of spraying a full dose of the composition into the nostril of an individual.

256. Barr's ANDA product meets each and every limitation of claim 13 of the '329 patent, as set forth below.

257. REDACTED

258. REDACTED

259. REDACTED

260. REDACTED

261. REDACTED

262. REDACTED

263. REDACTED

264. REDACTED

265. REDACTED

266. Dr. Berridge's PET studies by show that, when used according to the package insert, Nasacort® AQ deposits on each of the mucosal surfaces of the nasal cavity.

267. REDACTED

268. REDACTED

269. REDACTED

270. REDACTED

271. REDACTED

272. REDACTED

273. REDACTED

REDACTED

(b) Claim 14 of the '329 Patent

274. Claim 14 of the '329 patent covers:

> A method for treating allergic rhinitis in an individual comprising the administration to said individual of an aqueous thixotropic pharmaceutical composition comprising:
> (A) a pharmaceutically effective amount of solid particles of triamcinolone acetonide which is effective in treating allergic rhinitis by virtue of its being present on the mucosal surfaces of the nasal cavity of the individual; and
> (B) a suspending agent in an amount effective to maintain said particles dispersed uniformly in the composition and to impart to the composition thixotropic properties; by spraying a full dose of the composition in the form of a readily flowable atomized mist into one of the nostrils of the individual for deposit on the mucosal surfaces of the nasal cavity in the form of a viscous composition which resists being cleared from the mucosal surfaces by the inherent mucocillary forces which are present in the nasal cavity.

275. Use of Barr's ANDA product REDACTED , meets each and every limitation of claim 14 of the '329 patent, as set forth below.

276. Use of Barr's ANDA product REDACTED will cause users to infringe claim 14 of the '329 patent.

REDACTED

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REDACTED

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REDACTED

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291. REDACTED

292. REDACTED

293. REDACTED

294. REDACTED

(c) Claim 15 of the '329 Patent

295. Claim 15 of the '329 patent covers: "The method of claim 14 wherein said administration of said composition is performed once daily."

296. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 15 of the '329 patent, as set forth below.

297. Use of Barr's ANDA product REDACTED will cause users to infringe claim 15 of the '329 patent.

REDACTED

298. Use of Barr's ANDA product REDACTED ; meets each and every limitation of claim 14 of the '329 patent. (*See* ¶¶ 274-294).

299.

REDACTED

(d) Claim 16 of the '329 Patent

300. Claim 16 of the '329 patent covers: "The method of claim 15 wherein said once-a-day administration includes spraying multiple full doses of said composition."

301. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 16 of the '329 patent, as set forth below.

302. Use of Barr's ANDA product REDACTED labeling will cause users to infringe claim 16 of the '329 patent. REDACTED

REDACTED

303. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 15 of the '329 patent. (*See* ¶¶ 295-299).

304. REDACTED

(e) Claim 23 of the '329 Patent

305. Claim 23 of the '329 patent covers: "The method of claim 14 comprising spraying a full dose of about 55 mcg of said triamcinolone acetonide into said nostril of said individual."

306. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 23 of the '329 patent, as set forth below.

307. Use of Barr's ANDA product REDACTED will cause users to infringe claim 23 of the '329 patent.

REDACTED

308. Use of Barr's ANDA product according to Barr's proposed labeling meets each and every limitation of claim 14 of the '329 patent. (*See* ¶¶ 274-294).

309. Barr agrees that its proposed labeling directs users of its ANDA product to

REDACTED

(f) Claim 24 of the '329 Patent

310. Claim 24 of the '329 patent covers: "The method of claim 23 including spraying two of said full doses into said nostril once-a-day."

311. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 24 of the '329 patent, as set forth below.

312. Use of Barr's ANDA product will cause users to infringe claim 24 of the '329 patent. REDACTED

REDACTED

313. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 23 of the '329 patent. (*See* ¶¶ 305-309).

314.

REDACTED

(g) Claim 25 of the '329 Patent

315. Claim 25 of the '329 patent covers:

> A method for delivering an aqueous thixotropic pharmaceutical composition comprising triamcinolone acetonide to each of the mucosal surfaces of the anterior regions of the nose, the frontal sinus and the maxillary sinuses and on each of the mucosal surfaces which overlie the turbinates covering the conchas comprising spraying a full dose of the composition in the form of a readily flowable atomized mist into each nostril of the individual and allowing said sprayed composition to deposit on said surfaces in the form of a viscous composition which resists being cleared from the mucosal surfaces by the inherent mucocilliary forces which are present in the nasal cavity.

316. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 25 of the '329 patent, as set forth below.

317. Use of Barr's ANDA product REDACTED meets each and every limitation of claim 25 of the '329 patent.

318. Use of Barr's ANDA product REDACTED will cause users to infringe claim 25 of the '329 patent. REDACTED

REDACTED

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REDACTED

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REDACTED

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REDACTED

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REDACTED

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REDACTED

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REDACTED

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(h) Claim 26 of the '329 Patent

329. Claim 26 of the '329 patent covers:

> The method of claim 25 wherein said composition comprises about 1 to about 5 wt. % of a suspending agent comprising a mixture of about 85 to 95 wt. % of microcrystalline cellulose and about 5 to about 15 wt. % of carboxymethyl cellulose based on the weight of the mixture, the amount of suspending agent being effective to maintain said solid particles dispersed uniformly in the composition and to impart to the composition the following thixotropic properties: (i) the viscosity of the composition in unsheared form is about 400 to about 800 centipoise; (ii) as the composition is subjected to shear (shaken) in preparation for spraying, the viscosity of the composition is about 50 to about 200 centipoise.

330. Use of Barr's ANDA product , meets each and every limitation of claim 26 of the '329 patent, as set forth below.

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III. VALIDITY OF THE '573 AND '329 PATENTS

A. Proposed Conclusions of Law

341. Every claim of every issued patent is presumed valid. 35 U.S.C. § 282. A court begins its validity analysis by accepting the proposition that the patent is valid, and then looks to the accused infringer for evidence to the contrary. *Lear Siegler, Inc. v. Aeroquip Corp.*, 733 F.2d 881, 885 (Fed. Cir. 1984).

342. "[T]he burden of proving invalidity always remains with the party asserting invalidity; the burden never shifts to the patentee." *Harrington Mfg. Co. v. Powell Mfg. Co.*, 815 F.2d 1478, 1482 (Fed. Cir. 1986).

343. Patent invalidity must be proven by clear and convincing evidence. *Carella v. Starlight Archery & Pro Line Co.*, 804 F.2d 135, 138 (Fed. Cir. 1986); *TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004).

(1) 35 U.S.C. § 102(b)

344. If an accused infringer can establish by clear and convincing evidence that a claimed invention was "in public use . . . more than one year prior to the date of the application for patent," then that claim may be invalidated. 35 U.S.C. § 102(b).

345. A "'public use' for the purpose of barring access to the patent system is a use more than a year before the patent filing date, whereby a completed invention is used in public, without restriction and in circumstances other than 'substantially for the purposes of experiment.'" *Allied Colloids Inc., v. Am. Cyanamid Co.*, 64 F.3d 1570, 1574 (Fed. Cir. 1995); *see also Eli Lilly and Co. v. Zenith Goldline Pharms. Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006); *New Railhead Mfg., LLC. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1297 (Fed. Cir. 2002), *cert. denied* 537 U.S. 1232 (2003).

346. If a patent challenger makes a *prima facie* showing that a claimed invention was in "public use," then the patentee may negate this showing by demonstrating that the use of the invention was experimental. *Lough v. Brunswick Corp.*, 86 F.3d 1113, 1120 (Fed. Cir. 1996), *cert. denied*, 522 U.S. 806 (1997). Whether a use was a "public use" is a question of law, in which the accused infringer must prove the questions of fact by clear and convincing evidence. *Tone Bros. v. Sysco Corp.*, 28 F.3d 1192, 1197 n.3, n.4 (Fed. Cir. 1994), *cert. denied* 514 U.S. 1015 (1995).

347. An inventor is entitled to test his invention, potentially even in the open, without incurring the public use bar. "Experimental use negates public use; when proved, it may show that particular acts, even if apparently public in a colloquial sense, do not constitute a public use within the meaning of section 102." *Baxter Int'l Inc. v. Cobe Labs. Inc.*, 88 F.3d 1054, 1059 (Fed. Cir. 1996) (citing *TP Labs., Inc. v. Prof'l Positioners, Inc.*, 724 F.2d 965, 971 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 826 (1984).

348. In determining whether a use is a "public use" within the meaning of § 102(b), the court looks to the totality of the circumstances. The totality of the circumstances is

considered in conjunction with the policies underlying the public use bar. *Tone Bros., Inc.*, 28 F.3d at 1198.

349. In assessing experimentation, the Federal Circuit has considered "a number of factors, not all of which may apply in any particular case. These factors include: '(1) the necessity for public testing, (2) the amount of control over the experiment retained by the inventor, (3) the nature of the invention, (4) the length of the test period, (5) whether payment was made, (6) whether there was a secrecy obligation, (7) whether records of the experiment were kept, (8) who conducted the experiment, . . . (9) the degree of commercial exploitation during testing[,] . . . (10) whether the invention reasonably requires evaluation under actual conditions of use, (11) whether testing was systematically performed, (12) whether the inventor continually monitored the invention during testing, and (13) the nature of contacts made with potential customers.'" *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1353 (quoting *EZ Dock v. Schafer Sys., Inc.*, 276 F.3d 1347, 1357 (Fed. Cir. 2002)).

350. In the context of clinical trials on human patients, lack of confidentiality restrictions on the patients alone has not been held to establish that a use was a "public use." *See, e.g., Astrazeneca AB v. Mylan Labs, Inc.*, (*In re Omeprazole Patent Litig.*), 490 F. Supp. 2d 381, 508 (S.D.N.Y. 2007); *Eli Lilly and Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 912-13 (S.D. Ind. 2005); *Janssen Pharmaceutical N.V. v. Eon Labs Mfg., Inc.*, 374 F. Supp. 2d 263, 276 (E.D.N.Y. 2004), *aff'd by* 134 Fed. Appx. 425 (Fed. Cir. 2005); *Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 343 F. Supp. 2d 272, 307 (D. Del. 2004).

351. A new drug may not be marketed in the United States unless the FDA has first approved a New Drug Application ("NDA") or an Abbreviated New Drug Application ("ANDA") that covers that drug. 21 U.S.C. § 355(a).

352. Pursuant to FDA regulations, the contents of an NDA are kept confidential until the time of approval or abandonment of the NDA. 21 C.F.R. 314.430(b), (c).

353. The Federal Food, Drug and Cosmetic Act ("FFDCA") requires "adequate and well-controlled investigations" as a basis for approval of an NDA. 21 U.S.C. § 355(d).

354. In 21 C.F.R. 312.21(c), FDA defines a "Phase 3" study as follows:

> Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

355. FDA regulations provide that study protocols and other parts of an NDA will not be released if "the applicant shows that extraordinary circumstances exist." 21 C.F.R. 314.430(e). This reflects the underlying law, 21 U.S.C. § 505(l). As a general rule, FDA has accepted the position of innovators that extraordinary circumstances prevent the release of safety and effectiveness data. Even if the extraordinary circumstances exception is not effectively invoked, a protocol will still not be released if it is shown to be protected as a trade secret or confidential information. 21 C.F.R. 314.430(e)(3).

(2) 35 U.S.C. § 103

356. If an accused infringer can establish by clear and convincing evidence that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains," then that claim may be invalidated. 35 U.S.C. § 103.

357. The burden of proving invalidity is "most formidable" when the party asserting invalidity relies upon prior art already considered by the patent examiner. *Central Soya Co. v. Geo. A. Hormel & Co.*, 723 F.2d 1573, 1577 (Fed. Cir. 1983). *See also Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1378 (Fed. Cir. 2006) ("When the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity.") (citing *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990)).

358. Obviousness under § 103 is a question of law based upon underlying factual findings. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

359. In *Graham*, the Supreme Court set out a framework for applying that statutory language of § 103: "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." 383 U.S. at 17-18 (1966).

360. In *KSR Int'l Co. v. Teleflex Inc.*, the Supreme Court reaffirmed that "the [*Graham*] factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103." 127 S.Ct. 1727, 1734 (2007).

361. Even if all of the elements combined in a claimed invention are well known, the fact that elements work together in an unexpected manner supports a conclusion of nonobviousness. *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

362. A finding that a patented invention demonstrates superior and unexpected properties can establish nonobviousness. *American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350 (Fed. Cir. 1984). *See also Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1349 (Fed. Cir. 2004) (finding nonobviousness based on unexpected results); *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (same). The policy rationale for this is straightforward: something that would have been surprising to person of ordinary skill in a particular art probably would not have been obvious. *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1985).

363. In addition, nonobviousness may be established through a failure by the accused infringer to show a teaching, suggestion, or motivation to combine the elements. "When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1740 (internal citations omitted).

364. "A fact finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *Id.* at 1742 (citing *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the

prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight."))

365. "[A] flexible TSM [teaching-suggestion-motivation] test remains the primary guarantor against a non-statutory hindsight analysis . . . ." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, No. 2007-1223, 2008 U.S. App. LEXIS 6786, at *14-*15 (Fed. Cir. Mar. 31, 2008) (citing *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention.")).

366. "The TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence--teachings, suggestions (a tellingly broad term), or motivations (an equally broad term)--that arise before the time of invention as the statute requires." *Ortho-McNeil*, 2008 U.S. App. LEXIS 6786, at *15.

367. "Evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) (citation omitted). *See also Ortho-McNeil*, 2008 U.S. App. LEXIS 6786, at *16 ("this evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness") (citing *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

368. Without question, any objective indicia of nonobviousness must be considered, if they exist. *See WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed.

Cir. 1999) ("The consideration of the objective evidence presented by the patentee is a necessary part of the obviousness determination."); *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) ("The secondary considerations are . . . essential components of the obviousness determination."); *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986) ("Under *Graham*, objective evidence of nonobviousness includes commercial success, longfelt but unresolved need, failure of others, and copying. When present, such objective evidence must be considered.").

369. Objective indicia of nonobviousness "focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible of judicial treatment than are the highly technical facts often present in patent litigation." *Graham*, 383 U.S. at 36.

370. Secondary considerations provide objective evidence of the way interested industry actors perceived the claimed invention. *See Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072 (Fed. Cir. 1994) ("Such objective considerations are a useful guide in determining how a person of ordinary skill in the field would have viewed the patented invention at the time the invention was made."); *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991) ("Such objective indicia as commercial success, or filling an existing need, illuminate the technological and commercial environment of the inventor, and aid in understanding the state of the art at the time the invention was made."); *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988) ("The rationale for giving weight to the so-called 'secondary considerations' is that they provide objective evidence of how the patented device is viewed in the marketplace, by those directly interested in the product.").

371. For a secondary consideration to be accorded substantial probative value, its proponent must establish a "nexus" between the evidence and the merits of the claimed invention. *See In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention."); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 n.42 (Fed. Cir. 1985) ("Case law requires that a nexus be established between the merits of the claimed invention and the evidence proffered on secondary considerations, if the evidence on secondary considerations is to be given substantial weight in the calculus of obviousness/nonobviousness.").

372. An invention's commercial success presents strong evidence of nonobviousness. *See Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339 (Fed. Cir. 2004) (secondary consideration of commercial success favors the district court's nonobviousness determination); *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471 (Fed. Cir. 1986) ("Commercial success is . . . a strong factor favoring non-obviousness").

373. "[C]ommercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharms. USA*, 395 F.3d, 1364, 1376 (Fed. Cir. 2005).

374. "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). *See also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed.

Cir. 1988) ("A prima facie case . . . is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent.").

375. If the claimed invention solves a long-felt need, that also suggests that the invention was nonobvious. *Graham*, 383 U.S. at 17-18 (1966). *See also Glaxo Group Limited v. Apotex, Inc.*, 376 F.3d 1339 (Fed. Cir. 2004) (secondary consideration of "long felt but unresolved need" favors the district court's nonobviousness determination); *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573 (Fed. Cir. 1997); *Eli Lilly & Co. v. Generix Drug Sales, Inc.*, 324 F. Supp. 715, 717 (S.D. Fla. 1971), *aff'd*, 460 F.2d 1096 (5th Cir. 1972) (finding nonobviousness because "[t]he Pohland analgesic propoxyphene hydrochloride satisfied a long-felt need for a synthetic analgesic having the pain-relieving properties of morphine but without addiction liability.").

376. Prior failures by skilled artisans who attempted to achieve the claimed invention also suggests nonobviousness. *Graham*, 383 U.S. at 17-18. *See also Knoll Pharm.*, 367 F.3d at 1385; *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1572 (Fed. Cir. 1996).

377. Copying of the patented invention by others is another factor well established as probative of nonobviousness. *See Diamond Rubber Co. v. Consolidated Rubber Tire Co.*, 220 U.S. 428, 441 (1911) (copying "gives the tribute of its praise to the prior art; it gives the [invention] the tribute of its imitation, as others have done"); *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988) (stating that an accused infringer's close copying of the "claimed invention, rather than one in the public domain, is indicative of

nonobviousness"); *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285-86 (Fed. Cir. 2000) (quoting *Specialty Composites* with approval).

378. Evidence that a generic drug company decided to copy one brand name drug over another, or to copy a particular brand name drug when it could have copied other drugs not subject to patent protection, is significant evidence of nonobviousness. *See, e.g.*, *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006) (Farnan, J.) ("[t]he success of Lexapro® and its benefits compared with other SSRIs is also supported by the efforts of generic drug manufacturers, including Defendants, to copy the claimed invention"); *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 1088 (D. Del. 2005) (Farnan, J.) ("the fact that Ranbaxy has chosen to copy Lipitor® in its ANDA further demonstrates the success and efficacy of Lipitor® compared with other available products"), *rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006); *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 348 F. Supp. 2d 713, 759 (N.D. W.Va. 2004) ("the Court finds that Mylan's decision to copy LEVAQUIN instead of FLOXIN is significant evidence of non-obviousness, particularly in light of Mylan's lack of success in marketing its own respiratory quinolone"). *See also In re Certain Crystalline Cefadroxil Monohydrate*, 15 U.S.P.Q.2d 1263, 1271 (ITC 1990) (rejecting the argument that "copying should be accorded no weight in the obviousness determination because it is done solely to facilitate FDA approval").

379. 21 C.F.R. § 314.94(a)(9)(v) (2007), which is entitled "Inactive ingredient changes permitted in drug products," provides:

> Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the

> differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

380. 21 C.F.R. § 10.115(d)(1)-(2) (2007) provides:

> *Are you or FDA required to follow a guidance document?*
>
> (1) No. Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.
>
> (2) You may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with you to ensure that it complies with the relevant statutes and regulations.

(3) 35 U.S.C. § 112

381. The first paragraph of 35 U.S.C. § 112 provides that the patent specification must "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use" the claimed invention.

382. Under the enablement requirement, a patentee must disclose enough information that a skilled artisan would be able to practice the claimed invention without undue experimentation. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

383. In *In re Wands*, the Federal Circuit cited a number of factors that should be considered in determining whether a patent has provided enough detail to satisfy the enablement requirement, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance provided; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. 858 F.2d 731, 737 (Fed. Cir. 1988).

384. The relevant time frame for measuring enablement under § 112 is the date of filing the application. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991); *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The relevant time frame is not the time of trial. *Gould*, 822 F.2d 1074; *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Therefore, later occurring developments are of no significance regarding what one of skill in the art would believe as of the filing date. *In re Wright*, 999 F.2d 155 (Fed. Cir. 1993).

B. Proposed Findings of Fact

(1) 35 U.S.C. § 102(b)

(a) Experimental Use[1]

385. REDACTED

. Some of the results of those trials were later reported in Settipane et al. (1995) Clinical Therapeutics 17:252-63 ("Settipane") and Kobayashi et al. (1995) Clinical Therapeutics 17:503-13 ("Kobayashi"). However, as established in more detail below, those Phase 3 trials were an experimental use of the patented invention.

386. "Adequate and well-controlled investigations," pursuant to 21 U.S.C. § 355(d) often include Phase 3 studies, REDACTED

Phase 3 studies follow Phase 1 (preliminary studies, often in a few normal subjects, to determine whether the drug is unsafe to use in later trials) and Phase 2 studies (the first controlled clinical trials, usually in a relatively small number of subjects, to continue

[1] Barr recently argued unsuccessfully in another case that clinical trials were an invalidating public use. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, No. 05-cv-2308 (PGS), 2008 U.S. Dist. LEXIS 15917, at *110-28 (D.N.J. March 3, 2008).

determining safety and begin determining efficacy and dose ranging). Phase 3 studies attempt to establish the safety and efficacy of a drug in the general population.

387. REDACTED

388. REDACTED

389. The Phase 3 trial seasonal allergic rhinitis study (for which some results were reported in Settipane) was a placebo-controlled, double-blind study of 429 patients.

390. The Phase 3 trial perennial allergic rhinitis study (for which some results were reported in Kobayashi) was a placebo-controlled, double-blind study of 178 patients.

391. In the two placebo-controlled, double-blind Phase 3 studies, the clinical investigators did not know whether their patients were receiving the aqueous triamcinolone acetonide nasal spray or a placebo.

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Thus, no one could identify the individuals who received the aqueous triamcinolone acetonide nasal spray and those who received a placebo.

392. REDACTED

393. REDACTED

REDACTED

394. REDACTED

395. Barr agrees that the physicians conducting the clinical trial for which some results were reported in the Settipane article collected data relating to safety and efficacy of an aqueous TAA spray in patients with seasonal ragweed allergic rhinitis. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 219).

396. Barr agrees that the physicians conducting the clinical trial for which some results were reported in the Kobayashi article collected data relating to safety and efficacy of an aqueous TAA spray in patients with perennial allergic rhinitis. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 218).

397. Barr agrees that the physicians conducting the clinical trials for which some results were reported in the Settipane and Kobayashi articles kept regular reports regarding the progress of the trials. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 220).

398.

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399. REDACTED

400. REDACTED

401. The Phase 3 trials of Rhône-Poulenc Rorer's aqueous triamcinolone acetonide nasal spray had to be done in public to ensure that they accurately determined the safety and efficacy of the drug.

402.

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403.

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REDACTED

404. The claimed invention was a new formulation of an allergic rhinitis drug. It had to be tested *in vivo* and *in situ* to ensure both safety and efficacy.

405. REDACTED

406. Barr agrees that the clinical trial for which some results were reported in the Settipane article lasted approximately three weeks. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 223).

407. Barr agrees that the clinical trial for which some results were reported in the Kobayashi article lasted approximately four weeks. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 222).

408. In a Phase 3 trial, study participants generally do not pay for the medication being studied. Rather, the participants are often paid for their role, including following the study protocol for the administration of the experimental drug and reporting the results. That is especially true in a placebo-controlled trial, in which a substantial portion of the study participants (usually about half) receive a placebo instead of potentially efficacious therapy.

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409. REDACTED

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413. REDACTED

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415. The experimental aqueous triamcinolone acetonide nasal spray involved in the Phase 3 trials had to be evaluated under actual conditions of use. That is especially true because of the great likelihood that it would fail the Phase 3 trial, as about 40% of drugs do, including (notably in the intranasal drug field) doxepin, capsaicin, and tipredane formulations.

416. The Phase 3 trials were performed according to an extensive, detailed protocol with close monitoring to ensure adherence.

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418.

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419. Federal regulations required FDA to keep the results of Aventis's Phase 3 studies of Nasacort® AQ confidential prior to the approval of the NDA.

420. Even after an NDA is approved, it is often the case that protocols and other parts of an NDA will not be released to the public, though summaries of the results of the studies may be released.

(2) 35 U.S.C. § 103

(a) Scope and Content of the Prior Art

421. Some formulation of each of the products sold using the trademarks Beconase AQ®, Vancenase AQ®, Flonase®, Nasalide® and Nasacort® Nasal Inhaler was introduced in the United States more than one year before July 3, 1996. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 89).

422. Limited information for each of the products sold using the trademarks Beconase AQ®, Vancenase AQ®, Nasalide® and Nasacort® Nasal Inhaler is included in the 1995 Physician's Desk Reference ("'95 PDR"). (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 90). These PDR entries were before the PTO examiner when examining the applications from which the '573 and '329 patents issued.

423. Limited information for a product sold using the trademark Flonase® is included in the 1995 Physician's Desk Reference Supplement A ("'95 PDR Supplement A"). (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 91). This PDR entry was before the PTO examiner when examining the applications from which the '573 and '329 patents issued.

424. The active ingredient in Flonase® is fluticasone propionate. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 95).

425. The active ingredient in Beconase AQ® and Vancenase AQ® was beclomethasone dipropionate. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 96).

426. The active ingredient in Nasalide® is flunisolide. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 97).

427. Vancenase® AQ has been discontinued. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 100).

428. The prescribing information for Vancenase® AQ does not contain the word "thixotropic." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 158).

429. The package insert for Vancenase® AQ does not contain the word "thixotropic." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 159).

430. Schering Corp. and/or Schering Plough Corp. was the manufacturer of Vancenase® AQ. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 160).

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432. GlaxoSmithKline is the manufacturer of Beconase® AQ and Flonase®. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 162).

433. The prescribing information for Beconase® AQ does not contain the word "thixotropic." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 163).

434. The package insert for Beconase® AQ does not contain the word "thixotropic." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 164).

435. The prescribing information for Flonase® does not contain the word "thixotropic." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 165).

436. The package insert for Flonase® does not contain the word "thixotropic." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 166).

437.

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438. The Settipane, et al. article does not contain the phrases "propellant-free," "pH of about 4.5 to about 7.5," "a mixture of microcrystalline cellulose and carboxymethylcellulose sodium," "polysorbate 80," "disodium ethylenediamine tetraacetate," "benzalkonium chloride," and "dextrose." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 170).

439. The Settipane et al. article does not contain the phrase "Nasacort AQ." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 171).

440. The Kobayashi, et al. article does not contain the phrases "propellant-free," "pH of about 4.5 to about 7.5," "a mixture of microcrystalline cellulose and carboxymethylcellulose sodium," "polysorbate 80," "disodium ethylenediamine tetraacetate," "benzalkonium chloride," and "dextrose." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 172).

441. The Kobayashi et al. article does not contain the phrase "Nasacort AQ." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 173).

442. No composition discussed in U.S. Patent No. 4,767,612 ("the '612 patent") is described therein as being a thixotropic aqueous pharmaceutical composition. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 180).

443. The '612 patent does not describe a thixotropic aqueous nasal spray that is propellant-free. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 181).

444. The '612 patent does not state that a nasal spray has a pH of about 4.5 to 7.5. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 182).

445. The '612 patent does not describe a thixotropic aqueous nasal spray that includes a mixture of microcrystalline cellulose and carboxymethylcellulose sodium, Polysorbate 80, disodium ethylenediamine tetraacetate, benzalkonium chloride, dextrose, and purified water. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 184).

446. The 1995 Physicians' Desk Reference Supplement A was published on a different date from the 1995 Physicians' Desk Reference. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 185).

447. The 1995 Physicians' Desk Reference is a compendium of official, FDA-approved prescription drug labeling. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 186).

448. In the entries for Beconase AQ®, the '94 PDR and '95 PDR state: "Beconase AQ® Nasal Spray is a metered-dose, manual pump spray unit containing a microcrystalline suspension of beclomethasone dipropionate, monohydrate equivalent to 0.042% w/w beclomethasone dipropionate, calculated on the dried basis, in an aqueous medium containing microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% v/w phenylethyl alcohol." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 187).

449. In the entries for Vancenase AQ®, the '94 PDR and '95 PDR state: "Vancenase AQ® Nasal Spray is a metered-dose, manual pump spray unit containing a microcrystalline suspension of beclomethasone dipropionate, monohydrate equivalent to 0.042% w/w beclomethasone dipropionate calculated on the dried basis in an aqueous medium containing microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose,

benzalkonium chloride, polysorbate 80, and 0.25% v/w phenylethyl alcohol; hydrochloric acid may be added to adjust pH." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 189).

450. With respect to Nasalide®, the '94 PDR and '95 PDR entries state: "Each 25 mL spray bottle contains flunisolide 6.25 mg (0.25 mg/mL) in a solution of propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride, and purified water, with NaOH and/or HCl added to adjust the pH to approximately 5.3." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 191).

451. In the entry for Flonase®, the '95 PDR Supplement A states: "Flonase® Nasal Spray (0.05% w/w) is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 193).

452. No single aqueous nasal spray disclosed the '95 PDR is described therein as being a thixotropic aqueous pharmaceutical composition which (i) is capable of being sprayed into the nasal cavity of an individual, (ii) is propellant-free, (iii) has a pH of about 4.5 to 7.5, and (iv) includes triamcinolone acetonide. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 195).

453. No single aqueous nasal spray disclosed the '95 PDR is described therein as being a thixotropic aqueous pharmaceutical composition which (i) is capable of being sprayed into the nasal cavity of an individual, (ii) is propellant-free, (iii) has a pH of about 4.5 to 7.5, and (iv) includes (a) a mixture of microcrystalline cellulose and carboxymethylcellulose sodium; (b) polysorbate 80; (c) disodium ethylenediamine tetraacetate; (d) benzalkonium chloride; (e) dextrose; and (f) purified water. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 196).

454. No single aqueous nasal spray disclosed the '95 PDR is described therein as being a thixotropic aqueous pharmaceutical composition which (i) is capable of being sprayed into the nasal cavity of an individual, (ii) is propellant-free, (iii) has a pH of about 4.5 to 7.5, and (iv) includes (a) triamcinolone acetonide; (b) a mixture of microcrystalline cellulose and carboxymethylcellulose sodium; (c) polysorbate 80; (d) disodium ethylenediamine tetraacetate; (e) benzalkonium chloride; (f) dextrose; and (g) purified water. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 197).

455. No single aqueous nasal spray disclosed the '96 PDR is described therein as being a thixotropic aqueous pharmaceutical composition which (i) is capable of being sprayed into the nasal cavity of an individual, (ii) is propellant-free, (iii) has a pH of about 4.5 to 7.5, and (iv) includes triamcinolone acetonide. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 198).

456. No single aqueous nasal spray disclosed the '96 PDR is described therein as being a thixotropic aqueous pharmaceutical composition which (i) is capable of being sprayed into the nasal cavity of an individual, (ii) is propellant-free, (iii) has a pH of about 4.5 to 7.5, and (iv) includes (a) a mixture of microcrystalline cellulose and carboxymethylcellulose sodium; (b) polysorbate 80; (c) disodium ethylenediamine tetraacetate; (d) benzalkonium chloride; (e) dextrose; and (f) purified water. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 199).

457. None of the pharmaceutical compositions disclosed in PCT Application No. WO 92/14473 (the "'473 application") is described therein as including a chelating agent. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 202).

458. The '473 application does not contain the words "mucociliary clearance." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 203).

459. PCT Application No. WO 92/04365 (the "'365 application") does not contain the phrase "time dependent viscosity recovery." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 204).

460. The '365 application does not contain the phrase "mucociliary clearance." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 205).

461. The '365 application does not contain the words "once daily dosing." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 206).

462. PCT Application No. WO 94/05330 (the "'330 application") does not refer to once-daily dosing of any pharmaceutical composition disclosed therein. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 207).

463. Settipane, *et al.*, *Triamcinolone Acetonide Aqueous Nasal Spray in Patients with Seasonal Ragweed Allergic Rhinitis: A Placebo-Controlled, Double-Blind Study*, Clinical Therapeutics 17:252-263, 253 (1995), was before the PTO examiner when examining the applications from which the '573 and '329 patents issued. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 208).

464. Kobayashi, *et al.*, *Triamcinolone Acetonide Aqueous Nasal Spray for the Treatment of Patients with Perennial Allergic Rhinitis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study*, Clinical Therapeutics 17:503-513, 504 (1995), was before the PTO examiner when examining the applications from which the '573 and '329 patents issued. (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 209).

465. The PTO Examiner's conclusion in favor of patentability was made in part based on his belief that the claimed composition comprised "unique thixotropic properties, with

specific viscosity traits (sheared and/or unsheared), and further comprising triamcinolone acetonide as medicant." (*See* App. A, Parties' Statement of Uncontested Facts, ¶ 210).

(b) Differences Between the Prior Art and the Claimed Invention

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467. The Examiner's Reasons for Allowance, accompanying the '573 patent, states that the Examiner's conclusion in favor of patentability was made in part based on the claimed composition's "unique thixotropic properties, with specific viscosity traits."

468. During prosecution of the '573 patent, the Patent Examiner was aware of Flonase®; Beconase AQ®; Vancenase AQ®; and the Settipane and Kobayashi articles.

469. The specific viscosity profile recited in claim 5 of the '573 patent is completely absent from the entire body of prior art relied upon by Barr: Beconase AQ®; Vancenase AQ®; Flonase®; articles by Settipane, Kobayashi, and Pennington; and PCT Applications WO 92/14473, WO 92/04365, and WO 94/05330.

470.

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No other reference identifies a product with both an unsheared viscosity and a shear viscosity within the ranges required by claim 5 of the '573 patent and claim 26 of the '329

patent. Thus, that element of claim 5 of the '573 patent and claim 26 of the '329 patent (and all of the claims dependent upon them) is missing from the prior art.

471. In addition, there is no basis for determining that Beconase AQ® and Vancenase AQ® used a suspending agent that contains the relative amounts of microcrystalline cellulose and carboxymethylcellulose required by claim 5 of the '573 patent and claim 26 of the '329 patent (and all claims dependent therefrom).

472. REDACTED

473. REDACTED

474. REDACTED

475. REDACTED

In fact, numerous studies have confirmed that phenylethyl alcohol has an unpleasant odor that not only causes discomfort to patients, but also likely diminishes patient compliance with the treatment regimen due to such discomfort.

476. Prior to the invention claimed in the patents-in-suit, no aqueous intranasal steroid spray avoided burning, stinging, and irritation.

REDACTED Nasalide and Nasarel caused such side effects through polyethylene glycol and propylene glycol co-solvants.

477. No intranasal steroid suspension product prior to the invention claimed in the patents-in-suit used a chelating agent. In fact, no nasal suspension product (whether

including a steroid active ingredient or other active ingredient) used a chelating agent prior to the invention claimed in the patents-in-suit.

(i) Unexpected Results

478. The specifications of the patents-in-suit make clear that the combination of a quaternary ammonium compound and a chelating agent unexpectedly eliminates the need to employ an antioxidant to prevent degradation of triamcinolone acetonide in an aqueous environment. This function of the combination would not have been apparent to a person of ordinary skill in the art from reading a product ingredient list. No intranasal steroid suspension product prior to the invention claimed in the patents-in-suit used a combination of a quaternary ammonium compound and a chelating agent.

479. Barr seeks to rely upon Richards *et al.*, "Electron Microscope Study of Effect of Benzalkonium Chloride and Edetate Disodium on Cell Envelope of *Psuedomonas aeruginosa*," 65 J. Pharm. Sci. (1976) 65:76-70, to assert that the combination of a quaternary ammonium compound and a chelating agent would have been obvious. However, the Richards article is focused on electron microscopy, and is not one that a formulation scientist typically would consult.

480. The triamcinolone acetonide nasal spray formulations (and their use) described in the '573 and '329 patents demonstrate unexpected potency with fewer harmful side effects than Beconase AQ®, Vancenase AQ® or Flonase®. Triamcinolone acetonide is far less potent than fluticasone (the active pharmaceutical ingredient in Flonase®), yet the recommended starting dosage of Nasacort® AQ is about the same as that for Flonase®. Triamcinolone acetonide is also less potent than beclomethasone dipropionate (the active ingredient in Beconase

AQ® and Vancenase AQ®), but the recommended starting dosage of Nasacort® AQ is less than half that of Beconase AQ® and Vancenase AQ®.

481.

REDACTED

Nasacort® AQ does not use the combination of benzalkonium chloride and phenylethyl alcohol, and therefore its potency is even more surprising.

482. Beconase AQ® and Vancenase AQ® cause systemic side effects of diminished growth in children. The use of a less potent, less systemically available agent to achieve the same efficacy, which causes fewer side effects, is an unexpected benefit of the invention claimed in the patents-in-suit that would not have occurred to a person of ordinary skill in the art.

483.

REDACTED

484. Claim 5 of the '573 patent and its progeny, claim 35 of the '573 patent, and claim 26 of the '329 patent, indicate that Nasacort® AQ shows a difference in viscosity of potentially as small as 200 cp between the low end of the range for unsheared viscosity and the high end of the range for sheared viscosity. It is surprising that such a small difference between the two viscosity conditions can provide a product that exhibits long-term stability at rest, and desirable sprayability characteristics in sheared form.

(c) Level of Ordinary Skill in the Art

485. The hypothetical "person having ordinary skill in the art" would, in this case, likely be a team of two persons.

486. One member of the team would have experience in formulation of aqueous pharmaceutical compositions and an understanding of thixotropy and viscosity testing. That person could have a background in chemistry, chemical engineering, or pharmaceutical sciences, with experience dealing with formulation of aqueous pharmaceutical compositions, formulation of thixotropic aqueous compositions, and viscosity testing. That person could have a bachelor's degree with at least 3-5 years of experience in those areas; a masters degree with at least one or two years of experience in those areas; or a Ph.D. focused in those areas or an additional year of experience. That person would also need experience with a Brookfield LVT viscometer.

487. The second member of the team would have to be trained medically in the treatment of rhinitis and use of intranasal steroids. That person most likely would be a physician with at least one year of specialization in respiratory medicine. Alternatively, a nurse or medical technician with significant experience (at least three years) in nasal allergies and their treatment might qualify.

(d) Commercial Success

488. Nasacort® AQ, the commercial embodiment of the claims of the '573 and the '329 patents, is a commercial success. The commercial success of Nasacort® AQ is due to the specific elements of the invention recited in the claims of the '573 and the '329 patents.

489. Nasacort® Nasal Inhaler does not fall within the scope of the claims of the '573 and '329 patents.

490. REDACTED

491. REDACTED

492. The benefits of Nasacort® AQ include its thixotropic property, the lack of odor and taste, and patient comfort. These benefits are consistent with the benefits of the invention claimed by the patents in suit.

493. REDACTED

494. REDACTED

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511. REDACTED

(e) Long-Felt Need

512. There was a long-felt but unmet need for an aqueous nasal spray that had the combination of properties of being odorless, resisting clearance to the throat and/or mouth, having uniform dosing through a pre-compression pump, and being safe and effective for adults and children via once-daily dosing administration. Nasacort® AQ met this need.

513. There was a long-felt but unmet need for an aqueous nasal spray that resolved a persistent problem of patient compliance and dissatisfaction with INS-based nasal sprays. Nasacort® AQ met this need.

(f) Failure of Others

514. Tri-Nasal Spray was an aqueous intranasal spray that used the same intranasal corticosteroid, triamcinolone acetonide, as Nasacort® AQ. Additional similarities to Nasacort® AQ include that Tri-Nasal did not contain phenylethyl alcohol (in an attempt to be odorless) and that Tri-Nasal was to be taken as a once-daily dosing.

515. However, the formulation of Tri-Nasal was not identical to Nasacort® AQ, and the differences in formulation resulted in problems for the drug. For one, unlike Nasacort® AQ, which is a suspension, Tri-Nasal Spray is a solution. According to the Physicians' Desk Reference, like Nasalide, the Tri-Nasal solution contained polyethylene glycol 3350 and propylene glycol. Physician's Desk Reference (2002). Tri-Nasal had a 51% incidence rate of headaches among users, as indicated on their product insert. Furthermore, Tri-Nasal users reported sore throats and nasal irritation at much higher rates than Nasacort® AQ users. Patients also reported a taste perversion from Tri-Nasal Spray.

516. Tri-Nasal was launched in August 2000, and within less than a month after the launch, it was subject to a recall because of leaking containers. Tri-Nasal was re-launched a

year later, in 2001, and failed to capture even 1% of the market share. In 2002, Muro, the company that produced Tri-Nasal, sent communications to the public reporting that Tri-Nasal was being recalled, and withdrew it from the market place permanently. The FDA Enforcement Report associated with the recall stated that Tri-Nasal solution suffered from low potency of triamcinolone acetonide due to the fact that the formulation was unstable and the triamcinolone acetonide tended to precipitate out of the solution when subjected to cold temperatures, typically experienced during transit and storage. In 2002, the FDA withdrew its approval for Tri-Nasal Spray.

517. In 2003, Collegium Pharmaceuticals purchased the rights to Tri-Nasal Spray and announced its expectation of correcting the drug's deficiencies and relaunching the product. Collegium has not obtained FDA approval for any aqueous triamcinolone-containing nasal spray product to date. Thus, the only alternative formulation of an aqueous triamcinolone acetonide nasal spray failed.

(g) Copying

518. **REDACTED**

519. **REDACTED**

520. **REDACTED**

REDACTED

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REDACTED

528. REDACTED

529. Neither Agis nor Barr were required by statute, regulation or FDA guidance to copy Plaintiffs' formulation for Nasacort® AQ in order to obtain FDA approval for a generic version of Nasacort® AQ. In fact, the applicable regulations and FDA guidance

expressly permitted Barr to use different inactive ingredients in its generic version of Nasacort® AQ than those found in Nasacort® AQ.

530. The FDA has published two draft guidance documents entitled "Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action": one in June 1999 (the "1999 FDA Draft Guidance Document") and the other in April 2003 (the "2003 FDA Draft Guidance Document").

531.

REDACTED

532. In any event, the 1999 and 2003 Draft FDA Guidance Documents set forth only nonbinding *recommendations*, not requirements.

533. Publishing guidance documents is a method by which FDA provides its view on subjects when it is not addressing those subjects with binding rules. FDA's regulations concerning "good guidance practices" are very clear that there is no obligation to follow a guidance document. *See* 21 C.F.R. 10.115(d)(1)-(2).

534. FDA often, as in this case, first develops guidance documents in draft form. FDA then provides an opportunity for the public to submit comments on the draft. FDA may then alter the draft text before it issues a final guidance document. Because of the potential that it may be changed, there is less reason to follow the suggestions in a draft guidance document than there is to follow those set out in a final guidance document.

535. The 1999 FDA Draft Guidance Document and the 2003 FDA Draft Guidance Document provide recommendations for bioavailability and bioequivalence studies for

nasal aerosols and nasal sprays for local action, such as Barr's generic version of Aventis's Nasacort® AQ product. The 2003 document is an updated version of the 1999 document. FDA has not provided a further update since publishing the 2003 document.

536. Barr agrees that the 1999 and 2003 FDA Draft Guidance Documents contain recommendations. (*See* App. A, Parties' Statement of Uncontested Facts, ¶¶ 224-25).

537. Both guidance documents are draft documents. Both are marked "Draft – Not for Implementation." Each also states: "This guidance document is being distributed for comment purposes only." FDA has not issued final guidance for bioavailability and bioequivalence studies for nasal aerosols and nasal sprays.

538. Both the 1999 FDA Draft Guidance Document and the 2003 FDA Draft Guidance Document recommend that the inactive ingredients in a suspension formulation of a generic nasal spray, such as Barr's generic TAA nasal spray product, be qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the formulation of the reference listed drug. In addition, the 2003 document states: "Quantitatively *essentially the same* has been determined by CDER to mean that the concentration or amount of the inactive ingredient(s) in the test product would not differ by more than 5 percent of the concentration or amount in the reference listed drug." 2003 FDA Draft Guidance Document, p. 8.

539. Based on the 1999 and 2003 Draft Guidance Documents, copying Aventis's Nasacort® AQ formulation would have been the "path of least resistance" for Barr, at least in terms of FDA review. In other words, if Barr had submitted an ANDA with Nasacort® AQ as the reference listed drug, but Barr's formulation was not qualitatively the same and quantitatively essentially the same as Nasacort® AQ, then the FDA probably would have

scrutinized Barr's ANDA more carefully. Although not certain, FDA might have taken longer to approve Barr's ANDA.

540. Neither the 1999 FDA Draft Guidance Document nor the 2003 FDA Draft Guidance Document required Barr to copy Aventis's Nasacort® AQ formulation. In fact, both documents state that they contain nonbinding recommendations, not requirements. The 1999 document states: "This guidance represents the Agency's current thinking on product quality information related to inhalation aerosols and metered dose spray pumps for nasal delivery. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both." 1999 FDA Draft Guidance Document, p. 1, n. 1. Similarly, the 2003 FDA Draft Guidance Document states: "This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations." 2003 FDA Draft Guidance Document, p. 2.

541. In this case, there was even less reason than usual for a generic drug company to follow the 2003 FDA Draft Guidance Document because it was the second consecutive draft guidance document on the same topic. Ordinarily, FDA will issue guidance in draft form, receive comments, and then issue a final guidance. The fact that FDA issued a second consecutive draft guidance document on the same topic indicates that the 2003 FDA Draft Guidance Document is especially tentative.

542. In 2006, FDA responded to multiple citizen petitions concerning fluticasone propionate nasal spray suspension products (in a February 22, 2006 letter from

Randall W. Lutter, Ph.D., Acting Associate Commissioner for Policy and Planning, Food and Drug Administration, to Frederick H. Branding, C. Elaine Jones, Ph.D., William M. Zoffer and Charles J. Raubicheck, relating to docket nos. 2004P-0206/CP1; 2004P-0239/CP1, SUP 1, SUP 2 & PSA 1; 2004P-0348/CP1 & SUP 1; and 2004P-0523/CP1 & PSA1 ("2006 FDA Petition Response")). In that response, FDA directly addressed two petitions that asked FDA to convert its nonbinding recommendations in the 2003 FDA Draft Guidance Document into mandatory requirements. FDA rejected this request, stating: "FDA disagrees with Bell's and Frommer's petitions to the extent that they request FDA make mandatory the recommendations in the 2003 draft BA/BE guidance." 2006 FDA Petition Response, p. 3, n. 4. In the same response, FDA stated: "Guidance documents do not restrict FDA's ability to consider methodologies other than those articulated, nor do they restrict or replace the Agency's obligation to make a determination as to whether individual applications meet statutory requirements." *Id.*, p. 6 (referencing 21 C.F.R. § 10.115(d)). Thus, the 2006 FDA Petition Response makes it clear that the 1999 and 2003 Draft Guidance Documents contain only nonbinding recommendations.

543. No statute or regulation required Barr to copy Aventis's Nasacort® AQ formulation. In fact, the applicable regulation expressly states the opposite. *See* 21 C.F.R. § 314.94(a)(9)(v). The 2003 FDA Draft Guidance Document specifically refers to this regulation. *See* p. 8, n. 8. Thus, the applicable regulation expressly permits makers of generic nasal sprays to pursue FDA approval of formulations that are not qualitatively the same as the formulation of the reference listed drug.

544. Other competitors have copied aspects of the invention claimed in the '573 and the '329 patents, including Schering-Plough with their reformulated scent-free Nasonex product and GlaxoSmithKline with their once-daily, odorless Veramyst product.

(III) 35 U.S.C. § 112

545. The specifications of the '573 and '329 patents enable a person of ordinary skill in the art to make a nasal spray formulation that deposits on all of the regions of the nasal cavity recited in the asserted claims, including the frontal sinuses. (*See* ¶ 148).

546. The specifications of the '573 and '329 patents enable a person of ordinary skill in the art to make a nasal spray formulation that, following administration, is retained on all of the regions of the nasal cavity recited in the asserted claims, including the frontal sinuses, for at least about one hour. (*See* ¶ 148).

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